Adrenocorticotropic Hormone in the Treatment of Focal Segmental Glomerulosclerosis Following Kidney Transplantation

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ABSTRACT

This retrospective study examined the effect of adrenocorticotropic hormone therapy on remission of recurrent focal segmental glomerulosclerosis (FSGS) in patients with history of kidney transplant (KT) treated at 2 transplant centers. Patients with biopsy-confirmed FSGS following KT who received Acthar Gel (Mallinckrodt ARD, Bedminster, New Jersey, United States) treatment for ≥1 month were eligible. A total of 14 patients with idiopathic FSGS were included. Acthar Gel treatment resulted in complete remission of FSGS in 3 patients and partial remission in 2 patients for a total treatment response rate of 36% (5/14) of patients. Among patients showing complete or partial remission, Acthar Gel treatment duration ranged from 6 months to 2 years and 60% (3/5 patients) had serum creatinine ≤ 2 mg/dL at the start of Acthar Gel treatment. Patient outcomes suggest Acthar Gel may be an effective and tolerable treatment for recurrent FSGS in patients with history of KT. Early initiation of Acthar Gel treatment and therapy duration of at least 6 months may be needed for optimal response to Acthar Gel in patients with history of KT and recurrent FSGS.

PATIENTS with history of kidney transplant (KT) who have proteinuria in the nephrotic range have a high rate of graft loss, and recurrent nephrotic syndrome (NS) is a major cause of nephrotic-range proteinuria [1]. Excluding patients who had death with a functioning graft, out of 1505 patients with biopsy-confirmed glomerulonephritis, NS recurrence post-KT was the second-leading cause of allograft loss over 10 years, following chronic rejection [2]. In patients with idiopathic focal segmental glomerulosclerosis (FSGS), recurrence has been reported in up to 40% of patients with history of KT, increasing to 80% among patients with FSGS recurrence in a previous allograft, with 30% to 50% of these patients experiencing loss of their renal allograft [3,4]. Thus, there is an ongoing need for effective and tolerable treatments to optimize proteinuria reduction and graft survival in patients with a KT history and NS.

Currently, there are no guidelines or standard protocols for managing proteinuria in patients with recurrent NS following KT, and therapies such as renin-angiotensin-aldosterone system blockade, plasmapheresis, and immunosuppressive or cytotoxic regimens have shown inconsistent results, with unknown long-term efficacy and tolerability in patients with KT [5–7]. Acthar Gel is an adrenocorticotropic hormone that is a US Food and Drug administration–approved treatment to induce diuresis or remission of proteinuria in NS without uremia of the idiopathic type or in that due to lupus erythematosus. Adrenocorticotropic hormone has shown promise, with results demonstrating complete or partial remission of proteinuria in patients with NS of varied etiology in native kidneys [8–12]. Reports of the use of Acthar Gel in patients with recurrent NS post-KT have been previously reported in 2 case studies and a case review of patients with recurrent

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Table 1. Patient Demographic and Clinical Characteristics

Patient	Age* (y)	Sex	Race	KT Number	Donor	Pre-KT Diagnosis	Post-KT Diagnosis
1	42	M	W	1	LU	FSGS	FSGS
2	32	M	L	1	LU	FSGS	FSGS
3	35	M	AA	1	LU	FSGS	FSGS
4	32	F	W	1	LR	FSGS	FSGS
5	24	M	AA	2	D	FSGS	FSGS
6	59	F	AA	1	D	FSGS	FSGS
7	47	M	W	1	D	FSGS	FSGS
8	46	F	AA	1	LU	FSGS	FSGS
9	49	M	AA	1	LU	FSGS	FSGS
10	68	M	W	2	D	FSGS	FSGS
11	27	M	W	2	D	FSGS	FSGS
12	60	F	W	1	LR	FSGS	FSGS
13	16	M	AA	1	LR	FSGS†	FSGS
14	33	M	L	1	D	HTN‡	FSGS

Abbreviations: AA, African American; AS, Alport syndrome; D, deceased donor; F, female; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; KT, kidney transplant; L, Latino; LR, living related donor; LU, living unrelated donor; M, male; NS, nephrotic syndrome; W, White.
*Age at Acthar Gel initiation.
†FSGS diagnosis was not confirmed by biopsy.
‡Patient was presumed to have recurrent FSGS not confirmed by biopsy.

FSGS, and suggest effective proteinuria reduction [13–15]. In this retrospective study, we examined Acthar Gel therapy in patients with KT and posttransplant FSGS. We report the effect of Acthar Gel therapy on proteinuria and remission of FSGS, and the tolerability of Acthar Gel therapy in patients with history of KT. We also report the details of one case that serves as an illustration of the complexity of treating patients with KT and posttransplant FSGS.

METHODS

Patients at 2 transplant centers with biopsy-confirmed FSGS following KT who received Acthar Gel treatment for ≥1 month and had proteinuria assessed pre- and post-Acthar Gel were included in this retrospective chart review study. The institutional review board of the Georgetown-Howard Universities Center for Clinical and Translational Science and the Indiana University School of Medicine each approved this study. Patients enrolled from the Georgetown-Howard Universities Center for Clinical and Translational Science provided informed consent. Formal consent is not required by the Indiana University School of Medicine for this type of study. Patient demographic and clinical characteristics, KT-related induction and maintenance immunosuppressive therapies, FSGS treatment history, Acthar Gel dose, Acthar Gel treatment duration, adverse events (AEs), and allograft outcomes were collected from medical records. Renal function was evaluated using serum creatinine (SCr) level, with renal insufficiency defined as SCr $>$ 1.3 mg/dL. Proteinuria was assessed using urine protein-creatinine ratio (UPCR; g/g). Complete remission was defined as final UPCR $<$ 0.50 g/g and SCr $\leq$ 25% increase from pre-Acthar Gel treatment. Partial remission was defined as ≥50% reduction in proteinuria from pre-Acthar Gel treatment, final UPCR 0.50 to 3.50 g/g, and SCr $\leq$ 25% increase from pre-Acthar Gel treatment. Failure to meet criteria for complete or partial remission was defined as no response to Acthar Gel treatment. Patient data were summarized using percentages and descriptive statistics.

RESULTS

Among the 14 patients who met inclusion criteria, 71% (10/14) were male and 43% (6/14) were white (Table 1). Most patients

Table 2. Patient Treatment History Following Kidney Transplant

Patient	Induction Therapy	Treatment Prior to Acthar Gel	Maintenance Treatment at Acthar Gel Start	ACE-I/ARB at Acthar Gel Start
1	Alemtuzumab	PP, belatacept	MMF, prednisone	Y
2	Alemtuzumab	PP, abatacept	MMF, abatacept, prednisone	Y
3	Alemtuzumab	PP, belatacept	MMF, belatacept, prednisone	Y
4	Alemtuzumab	PP, abatacept	MMF, prednisone	N
5	Alemtuzumab	PP	MMF, tacrolimus	N
6	Alemtuzumab	PP, belatacept	MMF, tacrolimus	N
7	Alemtuzumab	PP	MMF, tacrolimus, prednisone	Y
8	Alemtuzumab	No treatment	MMF, tacrolimus	Y
9	ATG	Prednisone	MMF, tacrolimus, prednisone	Y
10	ATG	No treatment	MMF, tacrolimus	Y
11	ATG	PP, rituximab, prednisone	MMF, tacrolimus, prednisone	Y
12	ATG	PP, rituximab, prednisone	MMF, cyclosporine, prednisone	Y
13	ATG	No treatment	MMF, tacrolimus	N
14	ATG	PP	MMF, tacrolimus, prednisone	N

Abbreviations: ACE-I, angiotensin-converting enzyme-inhibitors; ARB, angiotensin II receptor blockers; ATG, antithymocyte globulin; MMF, mycophenolate mofetil; N, no; PP, plasmapheresis; Y, yes.

Table 3. Acthar Gel Treatment Outcome

Patient	Time From KT to Acthar Gel (d)	Time From FSGS Diagnosis to Acthar Gel (d)	Acthar Gel Duration (mo)	eGFR Pre-Acthar Gel, Post-Acthar Gel, % Change (cc/min)	SCr Pre-Acthar Gel, Post-Acthar Gel, % Change (mg/dL)	UPCR Pre-Acthar Gel, Post-Acthar Gel, % Change (g/g)	Acthar Gel Treatment Response	Graft Failure (Y/N; mo From End of Acthar Gel)
1	97	20	6	58, 77, +32.8	1.46, 1.16, -20.5	7.67, 0.60, -92.2	Partial remission	N
2	46	27	20	30, <10, -66.7	2.67, ESRD, NA	38.00, 10.00, -73.7	No response (↑SCr > 25%)	Y (0)
3	113	21	6	59, 47, -20.3	1.74, 2.13, +22.4	3.77, 1.30, -65.5	Partial remission	N
4	507	9	6	22, 12, -45.5	2.70, 4.63, +71.5	2.60, 2.60, 0	No response	Y (0)
5	45	22	2	<10, <10, 0	5.24, ESRD, NA	8.83, ESRD, NA	No response	Y (0)
6	19	7	24	43, 79, +83.7	1.48, 0.90, -39.2	3.12, 0.30, -90.4	Complete remission	N
7	340	311	1	27, <10, -63.0	2.72, ESRD, NA	7.65, 10.00, +30%	No response	Y (2)
8	1313	14	1	40, 39, -2.5	1.75, 1.81, +3.4	2.26, 2.26, 0	No response	NA
9	1602	122	2	25.7, 19.2, -25.3	3.80, 5.10, +34.2	5.70, 2.56, -55.1	No response (↑SCr > 25%)	Y (29)
10	1178	239	6	27, 40, +48.1	2.40, 1.99, -17.1	3.90, 3.06, -21.5	No response	N
11	1120	1048	7	56.1, 49.4, -11.9	1.12, 1.27, +13.4	4.64, 7.73, +66.6	No response	N
12	325	310	20	32, 30, -6.3	1.63, 1.73, +6.1	6.90, 6.57, -4.8	No response	Y (38)
13	0*	0*	6	18, 54, +200.0	3.49, 1.40, -59.9	3.50, 0.30, -91.4	Complete remission	N
14	14	5	6	37, 51, +37.8	2.08, 1.57, -24.5	3.3, 0.4, -87.9	Complete remission	N

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; KT, kidney transplant; N, no; NA, not available; SCr, serum creatinine; UPCR, urinary protein-creatinine ratio; Y, yes.

*Patient began Acthar Gel therapy prior to KT.

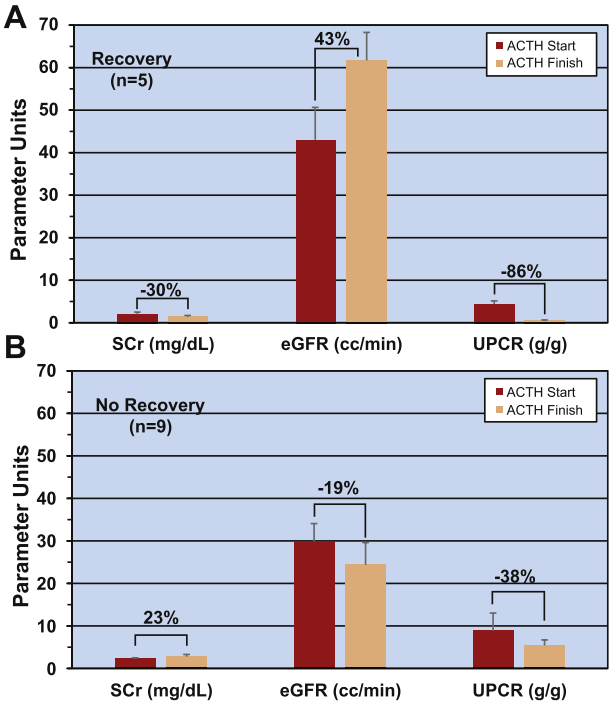

Fig 1. Effect of Acthar Gel treatment on serum creatinine (SCr), estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) in **(A)** patients showing partial or complete recovery (n = 5), and **(B)** patients showing no recovery (n = 9*). *Not all patients had values at the finish of Acthar Gel therapy. For SCr, n = 6; for eGFR, n = 9; for UPCR, n = 8. Only patients with values at both the start and finish of Acthar Gel therapy are represented above in Fig 1.

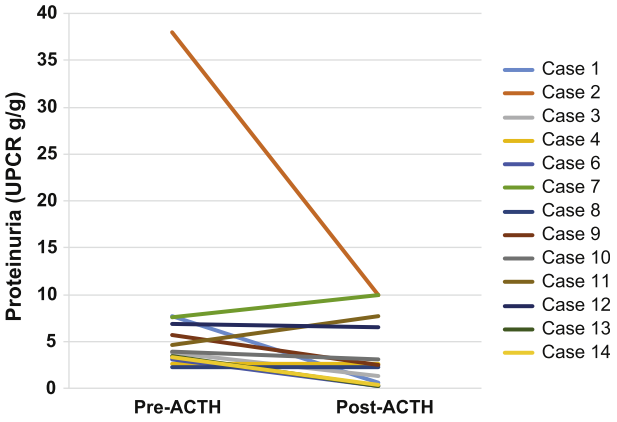

Fig 2. Individual changes in urine protein-creatinine ratio (UPCR, g/g) over the course of Acthar Gel therapy.* *Case 5 was in end-stage renal disease at the termination of Acthar Gel therapy and, therefore, unable to provide post–Acthar Gel UPCR values.

(79% [11/14]) underwent KT for the first time and 21% (3/14) had received a second transplant. Patients received kidneys from deceased donors (43% [6/14]), living unrelated donors (36% [5/14]), and living related donors (21% [3/14]). Mean age post-KT ± SD, at the start of Acthar Gel therapy, was 40.7 ± 14.9 years old (range, 16-68 years).

Induction immunotherapy included alemtuzumab (57% [8/14] of patients) and antithymocyte globulin (43% [6/14]). Ongoing maintenance immunosuppression (Table 2) included mycophenolate mofetil for all patients, tacrolimus for 64% (9/14) of patients, prednisone for 64% (9/14), and one patient each with abatacept, belatacept, and cyclosporine. Additionally, 64% (9/14) of patients received ongoing treatment with an angiotensin-converting enzyme-inhibitor (ACE-I) or angiotensin II receptor blocker. FSGS treatment prior to initiation of Acthar Gel (Table 2) included plasmapheresis (71% [10/14] of patients), high-dose prednisone (21% [3/14]), abatacept (14% [2/14]), belatacept (21% [3/14]), and rituximab (14% [2/14]), whereas 21% (3/14) of patients received no prior FSGS treatment except for standard center-based post-KT immunosuppression.

Time to initiation of Acthar Gel following KT varied across patients (Table 3), including 1 patient who began Acthar Gel therapy prior to KT (pediatric patient), 2 patients who began Acthar Gel 14 to 20 days following KT, another 4 patients who began Acthar Gel 21 to 113 days following KT, and 7 patients who initiated Acthar Gel from 325 days to 1602 days following KT. Excluding the patient who began Acthar Gel prior to KT, the time from FSGS diagnosis following KT to Acthar Gel initiation ranged from 5 to 1048 days. All patients received Acthar Gel 80 units twice per week. Duration of Acthar Gel treatment ranged from 1 to 24 months (median = 6.0) with 71% (10/14) of patients receiving Acthar Gel treatment for ≥6 months.

Proteinuria reduction following Acthar Gel treatment resulted in complete remission in 3 patients and partial remission in 2 patients for a total treatment response rate of 36% (5/14) of patients (Table 3). Among patients showing complete or partial remission, Acthar Gel treatment duration ranged from 6 months to 2 years and 60% (3/5 patients) had SCr ≤ 2 mg/dL at the start of Acthar Gel. Two patients (patients 2 and 9) showed large reductions in proteinuria (55% and 74%) but did not meet remission criteria due to SCr worsening >25%. Among the remaining 7 patients showing no response, Acthar Gel treatment duration was <6 months in 43% (3/7) of patients, 2 of whom discontinued treatment due to kidney failure. Among all 9 nonresponders, 67% (6/9) had SCr ≥ 2.4 mg/dL at treatment initiation. Overall, in those patients with available values, estimated glomerular filtration rate tended to be higher in patients with either a partial or complete response and increased over continued duration of Acthar Gel treatment (Fig 1). Patients showing no response tended to have lower estimated glomerular filtration, which declined further during Acthar Gel treatment. During Acthar Gel treatment, SCr tended to decline in patients demonstrating a response but increased in those who did not respond (Fig 1). UPCR tended to decrease, on average, in all patients over the course of Acthar Gel treatment but declined to a substantially greater degree in those patients who

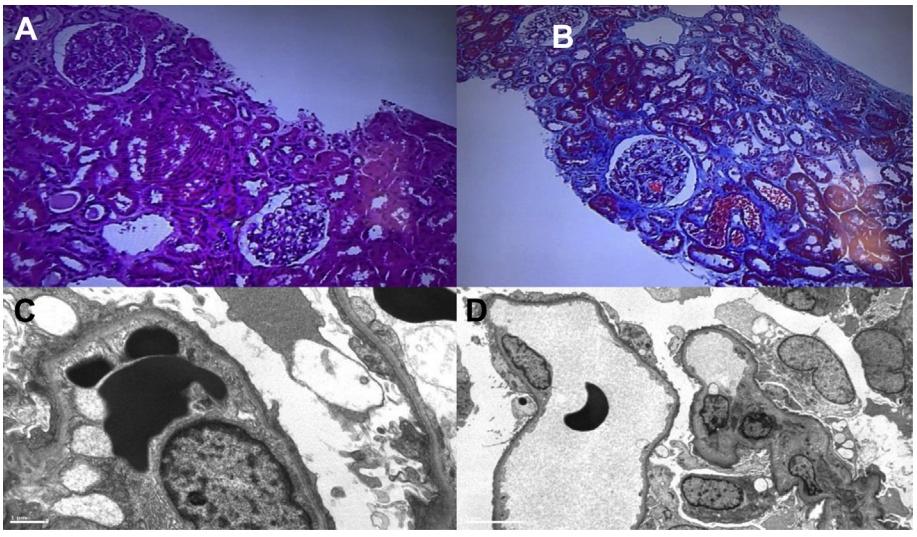

Fig 3. Renal biopsy approximately 1 month following transplant and prior to Acthar Gel therapy in a patient with recurrent focal segmental glomerulosclerosis (FSGS). **(A)** Hematoxylin and eosin (H & E) stain; **(B)** Trichrome stain; **(C)** Electron microscopy; **(D)** Electron microscopy.

showed a partial or complete response compared to those who did not respond (Fig 1, Fig 2).

Over the study period, graft failure occurred in 43% (6/14) of patients. AEs were reported by 29% (4/14) of patients during Acthar Gel therapy, including swelling or edema (2/14), tiredness or fatigue (1/14), diabetes (1/14), hyperglycemia (1/14), and weight gain (1/14). No patient discontinued Acthar Gel treatment due to AEs.

The complexities of treating recurrent FSGS post-KT are illustrated by patient 1, a white male who was 26 years old when first diagnosed with FSGS and 42 years old at the time of post-KT treatment with Acthar Gel. He had been briefly treated with prednisone and was receiving an ACE-I at the time of his pre-KT evaluation. He received the transplant, his first, from a living unrelated donor. Prior to KT, his proteinuria level was 27 g/day, which decreased to 2 g/day

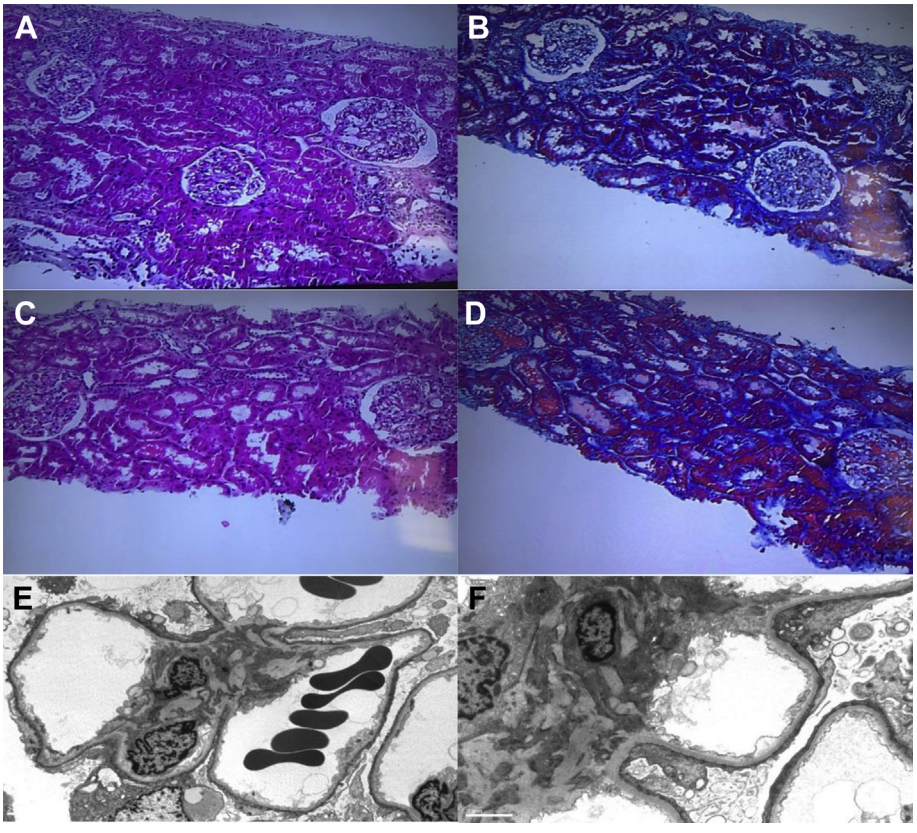

Fig 4. Renal biopsy in a patient with recurrent focal segmental glomerulosclerosis (FSGS). Upper panel: At the time of acute renal failure (consistent with a 1a rejection) following 6 months of Acthar Gel therapy. (**[A]** Hematoxylin and eosin [H & E] stain; **[B]** H & E stain.) Lower panel: Four months after acute renal failure. (**[C]** H & E stain; **[D]** H & E stain; **[E]** Electron microscopy; **[F]** Electron microscopy.)

immediately following KT, followed by an increase to 3 g/day in the first month following KT. Biopsy was delayed 1 month due to the patient's development of atrial fibrillation post-KT and treatment with anticoagulation for 1 month. Biopsy at 1 month post-KT showed recurrent FSGS (Fig 3). Approximately 2 months post-KT, he was started on belatacept, oral prednisone, lisinopril, and plasmapheresis 3 times per week for 2 months. At 3 months' post-KT, he started Acthar Gel 80 units twice per week and following 4 weeks of Acthar Gel therapy, he was successfully weaned from plasmapheresis. Following 6 months of Acthar Gel treatment, his UPCR decreased from 7.67 to 0.60 g/g, with SCr improving from 1.46 to 1.16 mg/dL. He met criteria for partial remission and Acthar Gel treatment was discontinued. At this time, he developed BK-virus viremia and his post-KT maintenance treatment with mycophenolate mofetil was decreased. He showed acute renal failure approximately 1 month later (Fig 4, upper panel), confirmed 4 months later (Fig 4, lower panel); however, he did not have graft failure.

DISCUSSION

Our report of Acthar Gel therapy for FSGS following KT suggests that Acthar Gel may be an effective and tolerable treatment for proteinuria reduction in patients with a history of KT and recurrent NS. Acthar Gel therapy was well tolerated by patients, with side effects similar to previous reports [8–12,14,15], and no patient required discontinuation of therapy due to side effects. Patients who had complete or partial remission of proteinuria were more likely than patients with no response to have lower SCr, indicating better renal function at initiation of Acthar Gel therapy, supporting perhaps the importance of early treatment to optimize proteinuria reduction in response to therapy. Additionally, the duration of Acthar Gel therapy in all 5 patients who showed complete or partial remission was 6 or more months. Acthar Gel was used as the initial therapy directed at FSGS post-KT in 3 patients. Of these patients, 1 showed complete remission and 1 had only received 1 month of ongoing Acthar Gel therapy at the time of the study. The patient with complete remission was a pediatric patient with recurrent FSGS who began Acthar Gel therapy prior to KT. Altogether, our findings suggest earlier onset of Acthar Gel treatment combined with therapy duration of at least 6 months may be needed for optimal response to Acthar Gel post-KT. In many of our patients, Acthar Gel was used as a "last resort," and the delay in initiation of Acthar Gel following FSGS recurrence may have underestimated its effectiveness in proteinuria reduction and support of graft survival.

Two previously reported cases have supported Acthar Gel effectiveness in recurrent FSGS following KT [13,14]. In both, patients with poor response to plasmapheresis and rituximab demonstrated significant proteinuria reduction following Acthar Gel therapy, and in one report, the patient achieved complete remission. In a recent retrospective review of similar cases ($n = 20$), patients showed significant improvement of UPCR after receiving Acthar Gel, and 50% achieved complete or partial remission [16]. It should be noted, however, that the Alhamad 2019 definitions [16] establish a lower threshold for partial remission (posttreatment proteinuria of 1-3.5 g/g, increase in creatinine $<30\%$) and complete remission (posttreatment proteinuria ≤ 1 g/g, increase in creatinine $<30\%$) than the definitions used in our study. Applying the Alhamad 2019 remission criteria to our patients would have resulted in 7/14 (50%) achieving complete or partial remission, equivalent to the finding in that study. Our patient outcomes of complete or partial remission in response to Acthar Gel therapy are consistent with other previous reports of the success of Acthar Gel treatment in recurrent FSGS, which defined remission thresholds similar to the ones used by us [8,10–12].

Although our success rate is not as dramatic as those previously reported, it should be kept in mind that these patients were already on existing dual or triple immunosuppressive drugs for prevention of graft rejection and the majority were on ACE/angiotensin II receptor blocker therapies. Most native kidney NS treatment protocols do not include combination immunosuppressive or other antiproteinuric therapies. Many immunosuppressive therapies such as mycophenolate or calcineurin inhibitors are quite often used in NS cases. The fact that these patients had FSGS while on this combination of agents suggests that these are high-risk patients with a likely high risk for graft failure. We observed that some cases with FSGS on conventional immunosuppressive agents responded to Acthar Gel, which suggests that the mechanism of action and pathogenesis of NS needs further investigation. Lastly, we find it an encouraging result that there were no other severe cases of infection noted while on concomitant Acthar Gel and immunosuppressive drugs.

The specific mechanisms of action by which Acthar Gel reduces proteinuria are not yet identified. Acthar Gel may have immunosuppressive and antiinflammatory effects and may have a direct podocyte-sparing effect in the glomerulus, possibly related to, but not limited to, activation of the melanocortin 1 receptor [17–23]. Patients with recurrent FSGS post-KT have shown diffuse podocyte foot process effacement, and the extent of effacement was associated with degree of proteinuria, implicating an important role of podocyte injury in recurrence [24]. Although the importance of podocyte injury is considered central to the disease pathogenesis of recurrent FSGS [22], the circulating factor responsible for podocyte injury, cytoskeleton reorganization, foot process effacement, proteinuria, and podocyte loss has yet to be identified [6,25].

Our retrospective study provides much needed clinical practice outcomes in the use of Acthar Gel therapy in patients with history of KT and FSGS following transplant. Limitations include the retrospective design, small number of patients, and lack of standardized study protocols for Acthar Gel and concurrent therapies. Additionally, there was no assessment of potential circulating biomarkers in our

patients. Our findings suggest further investigation of Acthar Gel in a prospective trial with larger patient groups, standardized protocols, and earlier treatment following NS recurrence is warranted. An important goal is the identification of patients who are most likely to benefit from Acthar Gel's treatment of recurrent NS following KT.

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